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BRIEF OBSERVATION

Safety of calcium antagonists: More ACTION

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As recently as 5 years ago, *The New York Times* reported that "the use of such drugs known as calcium channel blockers is leading to nearly 85 000 unnecessary heart attacks and cases of congestive heart failure each year worldwide."[1] This statement was based on a meta-analysis purporting to show that calcium antagonists, when compared with conventional drugs, increase the risk of myocardial infarction and congestive heart failure.[2] In contrast, the ALLHAT[3] study documented that the occurrence of coronary artery disease was virtually identical in the calcium antagonist, angiotensin-converting enzyme (ACE) inhibitor, and diuretic arm. Ironically, the meta-analysis in which the principal investigator of ALLHAT participated was published 5 years after the initiation of the ALLHAT study at a time when there was not a shred of evidence showing that calcium antagonists were harmful. The subsequent VALUE[4] study showed a better reduction of coronary artery disease in the amlodipine arm than in the valsartan arm, possibly because there was a difference in blood pressure favoring amlodipine. This, in a nutshell, set the stage for the ACTION study.[5]

ACTION was initiated in 1995, at the height of the calcium antagonist controversy.[6,7] At that time, short-acting formulations of nifedipine were considered harmful,[8] and there was no outcome evidence of long-acting calcium antagonist in coronary artery disease. ACTION clearly attested to the safety of calcium antagonists in such patients. There was no difference in all-cause death, cardiovascular death, noncardiovascular death, stroke, and myocardial infarction between nifedipine and placebo. New overt heart failure was better reduced with nifedipine than with placebo.

The authors of the ACTION study[5] are to be commended for thorough patient follow-up: Of the intended follow-up of 38 919 patient years, 97.3% were completed. Nifedipine caused a significant decrease in blood pressure throughout the ACTION study, which amounted to 6/2 mm Hg. Despite this, there was no reduction in the primary or secondary end point (with the exception of new overt congestive heart failure). On the basis of the decrease in systolic pressure, one can calculate the predicted versus observed odds ratio according to a metaregression model[9] (Table 1). For ACTION, the difference between predicted versus observed odds ratio was significant for cardiovascular events and myocardial infarction. In the much smaller PREVENT[10] and NICOLE[11,12] trials, similar to ACTION, patients with coronary artery disease (n = 825 and 826, respectively) were randomized to a calcium antagonist or placebo. The outcome results of PREVENT and NICOLE were almost identical to those of ACTION. Indeed, amlodipine and nisoldipine when compared with placebo failed to reduce the incidence of myocardial infarction (Table 1), although these drugs did decrease the risk of cardiovascular events, including unstable angina, congestive heart failure, stroke, and revascularization procedures. The recent CAMELOT[13] study comparing amlodipine or enalapril versus placebo in patients with coronary artery disease also showed very little benefit. Similar to the other above studies, the primary outcome results were mainly driven by coronary revascularization and hospitalization for angina. This brings up the question why blood pressure lowering with calcium antagonists did not reduce the risk of myocardial infarction in patients with coronary artery disease, particularly in the sufficiently powered ACTION trial?

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Table Predicted versus observed odds ratios for the ACTION, PREVENT, and NICOLE trials

	No. of events (control/experimental)	Predicted	Observed	*P* value
ACTION*				
CV death	177/178	0.81 (0.72–0.90)	1.01 (0.82–1.24)	.06
CV events	536/507	0.73 (0.67–0.80)	0.94 (0.85–1.05)	.0001
Stroke	99/77	0.68 (0.62–0.74)	0.78 (0.58–1.05)	.38
MI	257/267	0.76 (0.69–0.84)	1.04 (0.88–1.24)	.002
PREVENT*				
CV death	2/7	0.79 (0.71–0.88)	0.28 (0.03–1.46)	.22
CV events	30/24	0.71 (0.64–0.77)	0.77 (0.42–1.39)	.77
Stroke	5/5	0.66 (0.60–0.72)	0.98 (0.22–4.29)	.60
MI	20/19	0.74 (0.67–0.82)	0.76 (0.39–1.48)	.95
NICOLE*				
CV events	216/182	0.66 (0.60–0.72)	0.73 (0.55–0.97)	.48
Stroke	7/4	0.61 (0.55–0.67)	0.57 (0.12–2.27)	.93
MI	13/16	0.71 (0.64–0.79)	1.25 (0.56–2.86	.18

CV = cardiovascular; MI = myocardial infarction.

*ACTION, PREVENT, and NICOLE are acronyms of double-placebo controlled trials of nifedipine Gastrointestinal Therapeutic System, amlodipine, and nisoldipine in high-risk patients with preexisting coronary heart disease. The differences in achieved systolic blood pressure averaged 6.0, 6.8, and 9.1 mm Hg, respectively.

We think there could be several different reasons for this unexpected finding:

- Although in the ACTION trial, concomitant medication use was balanced at baseline, unequal use in the study could explain some of these findings (ie, more beta-blocker could have been used in the non-nifedipine arm).
- An incremental reduction in cardiovascular events is difficult to achieve in patients with coronary artery disease who are treated in a near-optimal way with antianginal, antihypertensive, and lipid-lowering therapy. Beta-blocker use was 80% in ACTION and 76% in CAMELOT compared with 52% in EUROPA[14] and 39% in HOPE.[15] The respective numbers for the use of lipid-lowering drugs were 68%, 83%, 57%, and 28%.
- For any given decrease in systolic pressure, calcium antagonists might be less effective in reducing the incidence of coronary artery disease than other drug classes, such as ACE inhibitors. Indeed, a recently completed meta-regression analysis confirmed that decreasing blood pressure is key to the prevention of cardiovascular complications, but it also showed small protective effects that were not dependent on blood pressure, which differed for calcium antagonists and ACE inhibitors with regard to stroke and coronary heart disease (unpublished observations).
- A decrease in diastolic pressure below a certain critical level could increase the risk of myocardial infarction in patients with coronary artery disease (J curve). Because coronary arteries are perfused during diastole only, a J curve, if any, should be most apparent for diastolic pressure and coronary artery disease. Indeed, we recently documented in the randomized INVEST study, with 22 000 patients, that the risk of primary outcome doubled in patients with diastolic pressures less than 70 mm Hg and quadrupled in patients with diastolic pressures less than 60 mm Hg.[16] No J curve was observed with systolic pressure and the primary outcome or with diastolic pressure and stroke. We concluded from the INVEST study that the preponderance of myocardial infarction over stroke at low diastolic pressure suggested that diastolic hypotension could impair coronary perfusion and increase the risk of coronary events in patients with coronary artery disease.[15]

In conclusion, ACTION established the safety of nifedipine in patients with stable angina. However, despite the decrease in blood pressure, nifedipine did not reduce the primary outcome or risk of myocardial infarction. Conceivably, the detrimental effect of a decrease in diastolic pressure could override the beneficial effect of a decrease in systolic pressure in this patient population with coronary artery disease (J curve). We therefore urge the ACTION investigators to thoroughly analyze the shape of the relationship between on-treatment diastolic pressure and the risk of coronary artery disease.

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